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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/807,132	04/06/2001	Masatsugu Maeda	14875-075001	4285

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EXAMINER	
WEGERT, SANDRA L	

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 06/15/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/807,132	MAEDA ET AL.	
	Examiner	Art Unit	
	Sandra Wegert	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 February 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8,10, 11 and 10-48* is/are pending in the application.

4a) Of the above claim(s) *10 and 11* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8 and 12-48* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *06 April 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of Application, Amendments, and/or Claims

The amendment filed 23 February 2004 has been entered. Claim 9 is canceled. Claims 10 and 11 were withdrawn by the Examiner (21 August 2003). Claims 13-48 have been added and read on the elected Invention.

Claims 1-8 and 12-48 are under examination.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a previous Office action.

Withdrawn Objections and/or Rejections

Title

The objection to the title as set forth at page 3 of the previous Office Action (21 August 2003) is *withdrawn* in view of the amendment which introduced a new title (23 February 2004).

URL's

The objection to the specification for sequence rules compliance is *withdrawn* in view of the amendment which added sequence identifiers to the short sequences in the figure legends (23 February 2004).

Claim Objections

The objection to Claims 1 and 12 for reciting non-elected subject matter (page 3, 21 August 2003) is *withdrawn*. Applicants amended Claims 1 and 12 to remove references to SEQ ID NO: 5, 6, 28, 29, 30 and 31 (23 February 2004).

Claim Rejections - 35 USC § 101, non-statutory.

The rejection of Claims 1, 4 and 12 under 35 U.S.C. 101, for embracing a product-of-nature, is *withdrawn*. Applicants amended Claims 1, 4 and 12 to add language indicating that the claimed subject matter is made "by the hand of man" (23 February 2004).

Claim Rejections - 35 USC § 112, second paragraph-indefiniteness.

The rejection of Claim 12 under 35 U.S.C. 112, second paragraph, as set forth at p. 14 of the previous Office Action, for reciting "highly stringent conditions" (21 August 2003) is *withdrawn* in view of the amendment that inserted into the claim specific stringency conditions supported by the Specification (23 February 2004).

Maintained Objections and/or Rejections

35 U.S.C. § 101/112, first paragraph-, Lack of Utility, Enablement.

Claims 1-8 and 12-48 are rejected under 35 U.S.C. 101, as lacking utility. The reasons for this rejection for Claims 1-6 and 12, under 35 U.S.C. § 101, are set forth at pp 4-11 of the previous Office Action (21 August 2003). Claims 1-8 and 12-48 are also

rejected under 35 U.S.C. § 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial utility or a well established utility for the reasons set forth in the previous Office Action (21 August 2003), one skilled in the art clearly would not know how to use the claimed invention.

It is noted that at pp 11-12 of the Response, the Applicant cites pertinent case law reviewing the current legal standards of what constitutes a specific and substantial utility for the claimed polynucleotides and polypeptides. The Examiner takes no issue with the Applicant's general comments regarding the legal standards for the levels of experimentation involved in utility and enablement of novel inventions. Issues specifically pertinent to utility of the instant invention, however, receive comment below:

Applicants assert that an enabling utility of the claimed invention is to be used as a tissue-specific marker:

"The present specification is rife with examples of the utility of the claimed invention. For example, the claimed GTAR14-1 nucleic acids and proteins exhibit tissue-specific expression patterns. mRNA for GTAR14-1 is observed only in the thymus during fetal development, and in testis, pancreas, and lymphatic/hematopoietic tissues including thymus and spleen in adults (see the specification at page 2, lines 32-35; page 6, lines 6-18; page 39, lines 22-25; and Fig. 7). A11 of these organs and tissues are known to be play a role in regulation of the lymphatic and endocrine systems" (Applicant's Response, 23 February 2004, page 12).

Applicants contend (23 February 2004, page 12) that being able to detect expression of GTAR14-1 in these tissues supports a utility of the claimed polynucleotides and polypeptides,

Applicant's arguments have been considered, but are not deemed to be persuasive. Contrary to the Applicant's contentions that these data provide "specific and substantial details of the claimed polynucleotides," it is difficult to associate a *specific* function with

a polypeptide that occurs in a multitude of normal, unrelated tissues. Nor is there a substantial function that can be associated with a polypeptide that is not associated -by tissue staining or otherwise- with a change in tissue function or with a disease state. Furthermore, the specification discloses a wide range of tissues that express the polypeptide of SEQ ID NO: 4. Applicants have demonstrated that the polypeptide of SEQ ID NO: 4 in the instant application is expressed in various tissues, including the thymus, testes, pancreas and spleen. Applicants imply that this expression supports a useful function of the polynucleotides encoding SEQ ID NO: 4 to be used "for developmental studies including cell fate experiments" (page 12). However, patentable utility of tissue typing for the claimed polynucleotides encoding the claimed polypeptides is not substantial because one skilled in the art would not readily use the nucleotide sequences for tissue-typing in a real world sense as the protein is not specific to one tissue and is not associated with any disease or disorder. This asserted utility is also not specific because numerous unrelated nucleotide sequences would also show a similar tissue-typing pattern. In addition, evidence of mere expression in a tissue is not tantamount to a showing of a role for the polynucleotides of the present invention. It is not clear if expression of the polynucleotide of the present Invention is correlated with a specific change in physiology, for example, or with a disease state. Since this asserted utility is not presented in mature form, so that it could be readily used in a real world sense, the asserted utility is not substantial.

Applicants then discuss the proposed utilities of antibodies that can be made against the olfactory receptor represented by SEQ ID NO: 4, and submit several

references that use methods in which cells or tissues are stained for detection of a specific protein (Forster et al., 1994, Blood 84(3):830-840; Cornish et al., 1989, B. J. Exp. Pathol. 70(5):495-504; Rocha et al., 1997, Blood, 89(6):2189-202). It should be kept in mind that papers and abstracts demonstrating proposed utilities for the instant peptides cannot be used as evidence to support a utility for the claimed peptides unless the experiments cited utilized the exact same polypeptide as SEQ ID NO: 4 in their functional experiments. Furthermore, very little information is given in the enclosed references- certainly not enough data to determine the *patentability* of the comparison peptides without more complete documentation. Lastly, as discussed in the previous Office Action (21 August 2003), the usefulness of antibodies rests on the utility of the protein against which they are made. The Specification fails to teach *which* activity is possessed by the disclosed full-length non-variant polypeptide encoded by SEQ ID NO: 1. For example, there is no discussion of specific drug ligands or unique endogenous ligands (e.g., odorants) for the olfactory receptor represented by SEQ IDS NO: 4, or the physiology of knockout or "knock-in" animals, or of transduction processes in cells transfected with SEQ ID NO: 1, or of disease states related to mutated receptors, to name a few examples.

The Applicant questioned the validity of the statement made in the previous Office Action (21 August 2003, p 4) that: "No well-established utility exists for newly-isolated complex biological molecules."

While the Examiner agrees that "genes and proteins are [ ] patentable under U.S. Law" (p. 14), one cannot use a "well-established utility" to assign a function to an unknown, new protein. This is because a "well-established utility" is one that is well-

known or well-established. And a "newly-isolated complex biological molecule" would, by definition, not be " well-known or well-established," at the time of its presentation in a patent application. For example, if one were to apply for a patent on human insulin or methods of using human insulin, little enabling data would need to be presented in the Specification concerning the utility of human insulin, since insulin has a "well-known or well-established" utility. Applicants have not referred to a "well-known or well-established" utility that existed for SEQ ID NO: 4 at the time of filing, and the Examiner has been unable to find references to such a utility from searching public databases and the scientific literature. Thus, one cannot assign a well-known or well-established function to the "newly-isolated complex biological molecule" that is the new protein of SEQ ID NO: 4 (see Applicant's Response, p. 14, 23 February 2004).

Brenner v. Manson (383 US 519) contemplated the utility of new inventions and concluded:

"The basic *quid pro quo* contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility. Unless and until a process is refined and developed to this point -- where specific benefit exists in currently available form -- there is insufficient justification for permitting an applicant to engross what may prove to be a broad field (Justice Fortas, writing for the majority)."

As stated in the conclusion: "A patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion (Justice Fortas)."

Applicants have not indicated or predicted a substantial or specific utility for the claimed polynucleotides or polypeptides.

Proper analysis of the Wands factors were provided in the previous Office Action. Due to the large quantity of experimentation necessary to determine an activity or property of the claimed polypeptide such that it can be determined how to use the claimed polypeptide or disclosed polynucleotide encoding the ion channel-like polypeptide and to screen for activity, the lack of direction/guidance presented in the specification regarding same, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art establishing that biological activity cannot be predicted based on structural similarity, the unpredictability of the effects of mutation on protein structure and function, and the breadth of the claims which fail to recite particular biological activities, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Furthermore, the Specification does not enable reasonably provide enablement for variants of SEQ ID NO: 4, as recited in Claims 1 and 3. The reasons for this rejection were set forth at pp. 10-11 of the previous Office Action (21 August 2003). The rejection centered on the lack of guidance regarding the specific activity of variants comprising SEQ ID NO: 4, and the lack of any working examples to variants of the claimed polypeptides. Applicants have not provided working examples in which variants of SEQ ID NO: 4 were made or used experimentally. The Applicant argues that, since the claims now specify that the fragments be "antigenic," that this substantially limits their structure and function (p. 16, 23 February 2001). However, specific activities of the protein of SEQ ID NO: 4 and fragments comprising are not disclosed. Furthermore, as discussed above, antibodies can be made to any protein. Therefore, use of the peptide as an antigen

is not an enabling function unless a specific function can be assigned to the full-length protein, such that it would be useful to make antibodies to the antigenic fragments. Applicants have not produced examples of peptide fragments or a representative number of species of the claimed fragments and tested them for function. Furthermore, since there is no discussion, or working examples disclosed in the instant case, as to what amino acids are necessary to maintain the functional characteristics of the disclosed polypeptides, the polynucleotides encoding the fragments are also not useful. In addition, it is not known the *expected* function that such fragments would possess, since the full-length receptor polypeptide has not been shown to have a specific function.

35 U.S.C. 112, first paragraph- Written Description

The rejection of Claims 1-6 under 35 U.S.C. 112, first paragraph, for lack of Written Description is *maintained.* In addition, the rejection of Claims 8 and 43 under 35 U.S.C. 112, first paragraph, for lack of Written Description of the claimed methods is *maintained.* This rejection was made at pages 11-14 of the previous Office Action (21 August 2003), because the claimed subject matter was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

Applicants argue (23 February 2004) that amino acids are highly-tolerant of residue changes. Therefore, if the Specification teaches which variants to make and how to use them, the Written Description requirement will be satisfied. However, Claims 1-6, 8 and 43 are directed to methods of using SEQ ID NO: 4 when they encompasses an

unknown number of polypeptides, and utilizing proteins comprising proposed mutations that would result in substitution or deletion of processing sites on the receptor polypeptide, the results of which would be unexpected.

The specification teaches GTAR14-1 (SEQ ID NO: 4). However, the specification does not teach functional or structural characteristics of all possible GTAR14-1 polypeptides encompassed by the claims. The description of one GTAR14-1 polypeptide species is not adequate written description of an entire genus of functionally equivalent polypeptides. Applicants have not made and tested all possible encompassed variants of SEQ ID NO: 4 in the described experimental assays, nor even tested a representative subset of possible encompassed variants of SEQ ID NO: 4, and shown they function identically.

Applicants have argued (page 17, Response; 23 February 2004) that individual amino acids, as well as large domains of G-protein-coupled receptors can be exchanged "with little likelihood of losing the 'G-protein coupled receptor' function of the protein" (Gershengorn and Osman, 2001, Endocrinology 142(1):2-10; Ji et al., 1998, J. Biol. Chem. 273(28):17299-17302; Postina et al., 1998, Adv. Exp. Med. Biol. 449:371-385; Bowie et al, 1990, Science 247:1306-1310). However, it is not known the specific function of SEQ ID NO: 4 referred to by the Applicant, since functional experiments were not performed. It is difficult to evaluate whether mutated proteins based on SEQ ID NO: 4 would maintain the same function without some evidence of representative species of proteins produced and tested for a specific substantial function (i.e., a function other than "G-protein-coupled receptor"). Applicants discuss data from Bowie, et al (1990, Science 247:1306-1310) in which single amino acid substitutions were made in the *lac*

repressor, stating: "Of approximately 1500 single amino acid substitutions at 142 positions in this protein, about one-half of the substitutions were found to be 'phenotypically silent,' i.e., had no noticeable effect on the activity of the protein. [ ] Thus, one can expect, based on Bowie et al.'s teachings, to find over half and possibly well over half of random substitutions in any given protein to result in proteins with full or nearly full activity" (Response, 23 February 2004, p. 17). However, the Bowie paper demonstrates dramatically the effect of seemingly minor mutations on a protein's function. That research group performed only *single* amino acid substitutions, and still changed the function of the described protein *half* the time. Each mutant protein they produced, then, is potentially a distinct protein. It should be kept in mind that Claims 1-6 in the instant Specification encompass proteins with up to 30 amino acid substitutions, as well as deletions; therefore, the potential to destroy or change the function of SEQ ID NO: 4 can be expected to be greater than 50% (see also Wells, J.A., 1990, Additivity of Mutational Effects in Proteins. Biochem, 29(37): 8509-8517, esp. Table II).

To provide evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In this case, the only factor present in the claims is a recitation of nucleotide bases present in SEQ ID NO: 3 and amino acids of SEQ ID NO: 4, as well as the proposed substitution or deletion of one to thirty residues. There is not even identification of any particular portion of the structure that must be conserved (for example, to maintain function). In the absence of a sufficient

recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus. Making and using a representative number of fragments of SEQ ID NO: 4 are likewise not adequately described.

Applicants cite the *Wands* Case (8USPQ2d, 1400 (CAFC 1988) page 1404, Docket 87-1454), stating that "[t]hese are far better odds than those at issue in In re Wands," referring to Written Description for the claimed fragments of SEQ ID NO: 4 and methods of using modified GTAR14-1 polypeptides. *Wands* concerned the scope of claims that may be made to antibodies. That case put forth arguments showing how the number of antibodies that may be claimed to a polypeptide sequence is essentially unlimited. Applicants imply that the same evaluation applies to the claimed method of making and using GTAR14-1 polypeptides.

Applicant's arguments have been fully considered but are not deemed to be persuasive for the following reasons:

The fact patterns in the *Wands* case are substantially different than those pertaining to the instant Application. Since antibodies are made by unknown and random recombinations of a B-cell's genome- which may yield a large number of possible antibodies that bind the same peptide, and because it is not known and not predictable what the exact epitope/antibody binding configuration is, as well as the fact that antibodies are claimed and patented in reference to the *one* specific polypeptide against which they are made- it is not practical to require Applicants to define an antibody invention in terms of the antibody *sequence*. An applicant may therefore patent all antibodies that bind to *one* particular polypeptide or epitope. Since the *Wands* case applies only to the scope of claims that may be made to *antibodies* in a patent application,

it is not applicable to the method of making and using variant GTAR14-1 polypeptides.

New Objections/Rejections

Claim Objections

Claims 18 and 21 are objected to for reciting non-elected subject matter: "the transformant," because this phrase encompasses transgenic animals. Amending the claims to recite "the transformed cell," for example, would be remedial.

Appropriate correction is required.

Claim Rejections - 35 USC § 112, second paragraph-indefiniteness.

Claims 18, 19, 20, 22, 23, 32, 33, 34 and 47 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 18 is indefinite for reciting "carrying," as in "carrying the DNA." The metes and bounds of "carrying" cannot be determined from the claim since it is unclear if this refers to *carrying* as used in everyday language, or *consisting of* or *comprising* the DNA. Amending the claims to recite "comprising," for example, would be remedial.

Claims 19, 20, 22, 23, 32, 33, 34 and 47 are indefinite for reciting a "host cell." The metes and bounds of a "host cell" cannot be determined from the claims since it is unclear if the claims are limited to an isolated host cell or a host cell in the context of a transgenic organism including, possibly, a human.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Advisory information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sandra Wegert whose telephone number is (571) 272-0895. The examiner can normally be reached Monday - Friday from 9:00 AM to 5:00 PM (Eastern Time). If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Gary Kunz, can be reached at (571) 272-0887.

The fax number for the organization where this application or proceeding is

assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

SLW
6/9/04

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